

# Constrictive Pericarditis in the Modern Era

## Novel Criteria for Diagnosis in the Cardiac Catheterization Laboratory

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### Objectives

This study sought to determine the clinical utility of a new catheterization criterion for the diagnosis of constrictive pericarditis (CP).

### Background

The finding of early rapid filling and equalization of end-diastolic pressures obtained by cardiac catheterization are necessary for the diagnosis of CP, but these findings are also present in patients with restrictive myocardial disease (RMD). Enhanced ventricular interaction is unique to CP.

### Methods

High-fidelity intracardiac pressure waveforms from 100 consecutive patients undergoing hemodynamic catheterization for diagnosis of CP versus RMD were examined. Fifty-nine patients had surgically documented CP and comprised group 1; the remaining 41 patients with RMD comprised group 2. The ratio of the right ventricular to left ventricular systolic pressure-time area during inspiration versus expiration (systolic area index) was used as a measurement of enhanced ventricular interaction.

### Results

There were statistically significant differences in the conventional catheterization criteria between CP and RMD, but the predictive accuracy of any of the criteria was <75%. The systolic area index had a sensitivity of 97% and a predictive accuracy of 100% for the identification of patients with surgically proven CP.

### Conclusions

The ratio of right ventricular to left ventricular systolic area during inspiration and expiration is a reliable catheterization criterion for differentiating CP from RMD, which incorporates the concept of enhanced ventricular interdependence. (J Am Coll Cardiol 2008;51:315-9) © 2008 by the American College of Cardiology Foundation

The differentiation of constrictive pericarditis (CP) from restrictive myocardial disease (RMD) remains difficult. Two-dimensional and Doppler echocardiography, visualization of the pericardium by computed tomography or magnetic resonance imaging, and conventional cardiac catheterization have been useful in this differential diagnosis, but the diagnosis remains equivocal after extensive testing in a subset of patients (1-4). This study examines the clinical utility of a new catheterization criterion in 100 consecutive patients, which incorporates the concept of ventricular interaction (5).

### Methods

**Patient population.** The patient population consisted of 100 sequential patients referred to the cardiac catheterization laboratory at the Mayo Clinic (Rochester, Minnesota) for hemodynamic evaluation of CP versus RMD from July 1997 to November 2004. All patients had symptoms of

right heart failure and findings of elevated venous pressure in the absence of severe left heart disease. The protocol was approved by the Institutional Review Board of the Mayo Clinic.

Based on the results of the clinical evaluation and catheterization results, 61 patients were sent to exploratory surgery and all underwent complete pericardiectomy. Operative reports were reviewed to confirm a surgical description of CP, specifically the presence of obliteration of the pericardial space, bulging of the heart on incision of the pericardium, the presence of an abnormal pericardial (thickening and/or calcification), and a post-operative decrease in right atrial pressure (RAP) and increase in cardiac index. The remaining patients were diagnosed with other causes of heart failure after undergoing a comprehensive cardiac evaluation, including a subset of these patients (n = 23) who underwent right ventricular (RV) endomyocardial biopsy when the final diagnosis was unclear from the diagnostic studies.

**Hemodynamic cardiac catheterization.** A standardized cardiac catheterization was performed in all patients lightly sedated in the fasting state. In patients with atrial fibrillation,

## Abbreviations and Acronyms

**CP** = constrictive pericarditis  
**LV** = left ventricle/ventricular  
**LVEDP** = left ventricular end-diastolic pressure  
**RAP** = right atrial pressure  
**RMD** = restrictive myocardial disease  
**RV** = right ventricle/ventricular  
**RVEDP** = right ventricular end-diastolic pressure

overdrive ventricular pacing with a temporary pacemaker was used to ensure a regular rhythm (5). High-fidelity, micromanometer-tipped catheters (Millar Instruments, Houston, Texas) were used to obtain right-sided and left-sided cardiac pressure waveforms as previously described (5), balanced with fluid-filled pressures. All right-sided pressure measurements were recorded simultaneously with left ventricular (LV) pressure. The pressure records were recorded during normal quiet respiration (for measurement of end-expiratory pressures) and

then during exaggerated respiration, with an inspiratory decrease in the minimum diastolic pressure  $>8$  to 10 mm Hg. Volume loading of 1 liter normal saline was performed in patients who had been previously treated with diuretics and were found to have RAP ( $<15$  mm Hg) (6).

**Analysis of pressures.** Baseline pressure waveforms from high-fidelity catheters were measured simultaneously in the right and left sides of the heart at end-expiration during normal quiet respiration, using an average of 3 to 5 consecutive beats. These measurements are shown in Table 1 and included RAP, pulmonary artery systolic pressure, right ventricular end-diastolic pressure (RVEDP), pulmonary capillary wedge pressure, left ventricular end-diastolic pressure (LVEDP), and height of the rapid filling wave (Table 1). Conventional hemodynamic criteria for the differentiation of CP from RMD have relied on the relationship between RVEDP and LVEDP, as well as the secondary effect on pulmonary pressures (4,7-9), and are outlined in Table 2.

**Table 1** Hemodynamic Measurements at Cardiac Catheterization

Measurement	Group 1 (n = 59)	Group 2 (n = 41)	p Value
Heart rate (beats/min)	81 $\pm$ 17	75 $\pm$ 13	p < .05
SBP (mm Hg)	102 $\pm$ 18	126 $\pm$ 25	p < .001
Peak PASP (mm Hg)	44 $\pm$ 11	47 $\pm$ 15	p = NS
LVEDP (mm Hg)	21 $\pm$ 7	18 $\pm$ 7	p < .05
RVEDP (mm Hg)	21 $\pm$ 7	15 $\pm$ 6	p < .001
LVRFW (mm Hg)	7.4 $\pm$ 1.9	6.5 $\pm$ 1.1	p = NS
Inspiratory decrease in RAP (mm Hg)	3.0 $\pm$ 1.7	4.4 $\pm$ 3.1	p < .02
LVEDP - RVEDP (mm Hg)	4.5 $\pm$ 0.6	6.4 $\pm$ 1.2	p < .05
RVEDP/RVSP	0.50 $\pm$ 0.13	0.35 $\pm$ 0.14	p < .001
Systolic area index	1.4 $\pm$ 0.2	0.92 $\pm$ 0.19	p < .0001

Group 1 = constrictive pericarditis; Group 2 = restrictive myocardial disease; LVEDP = left ventricular end-diastolic pressure; LVRFW = left ventricular height of rapid filling wave; PASP = pulmonary artery systolic pressure; RAP = right atrial pressure; RVEDP = right ventricular end-diastolic pressure; RVSP = right ventricular systolic pressure; SBP = systolic blood pressure.

**Table 2** Catheterization Criterion

Criterion	Sensitivity (%)	Specificity (%)	Positive Predictive Accuracy (%)	Negative Predictive Accuracy (%)
LVEDP - RVEDP $\leq 5$ mm Hg	46	54	58	40
PASP $< 55$ mm Hg	90	29	73	66
RVEDP/RVSP $> 1/3$	93	46	71	79
LVRFW $> 7$ mm Hg	45	44	62	42
Inspiratory decrease in RAP $< 5$ mm Hg	71	37	62	39
Systolic area index $> 1.1$	97	100	100	95

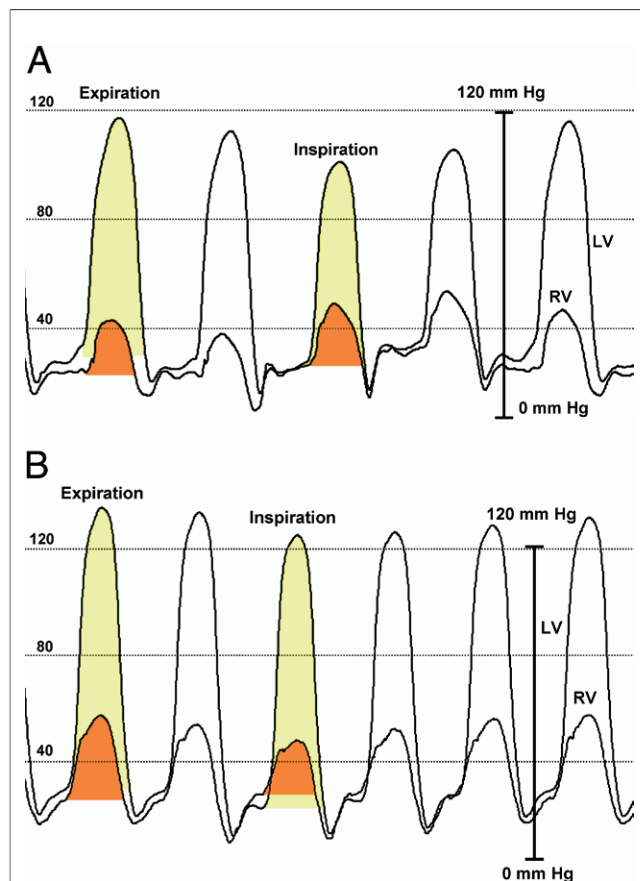
Abbreviations as in Table 1.

Analysis of the pressure waveforms were then made during exaggerated respiration. The peak inspiratory beat was selected as the systolic impulse that was preceded by the lowest early diastolic nadir of the LV pressures (Fig. 1). Selection of the peak inspiratory beat required that the early diastolic nadir was at a minimum for the diastolic filling period before and after the systolic pressure contours. The peak expiratory beat was selected as the systolic impulse that was preceded by the highest early diastolic nadir of the LV pressure. In patients with CP, there is an inspiratory decrease in the LV volume and enhancement of ventricular coupling so that there is an obligatory increase in volume of the RV (1,5). The LV pressure curves become smaller in terms of both the height and width of the curve, and the RV pressure curve becomes larger during peak inspiration in patients with CP. Previously, the use of a RV index based on RV peak systolic pressure variation between inspiration and expiration was used as a measure of ventricular coupling (5). We subsequently found that changes in the peak pressure alone were not sensitive enough to detect all patients with CP. Therefore, the area under the ventricular pressure curve was used to determine the change in the relative volumes of the LV and RV, which is a better determinant of beat-to-beat stroke volume than the peak pressure alone (Fig. 1). The systolic area index was defined as the ratio of the RV area (mm Hg  $\times$  s) to the LV area (mm Hg  $\times$  s) in inspiration versus expiration.

**Statistical analysis.** Data are expressed as mean  $\pm$  SD. The unpaired *t* test was used to compare continuous variables between the 2 groups. The Fisher exact test was used to compare nominal variables between the 2 groups. Pre-operative and post-operative comparisons were made using matched pairs analysis. Statistical significance was predefined as p < 0.05. All statistical calculations were performed using JMP 5.1 software (SAS Institute, Cary, North Carolina).

## Results

**Patient characteristics.** Of the 100 patients presenting to the cardiac catheterization laboratory for the differentiation of CP versus RMD, 61 went to exploratory thoracotomy. Fifty-nine had surgically documented CP (group 1). There



**Figure 1** LV and RV High-Fidelity Manometer Pressure Traces From 2 Patients During Expiration and Inspiration

Note that both patients have early rapid filling and elevation and end-equalization of the left ventricular (LV) and right ventricular (RV) pressures at end expiration. (A) A patient with surgically documented constrictive pericarditis. During inspiration there is an increase in the area of the RV pressure curve (orange shaded area) compared with expiration. The area of the LV pressure curve (yellow shaded area) decreases during inspiration as compared with expiration. (B) A patient with restrictive myocardial disease documented by endomyocardial biopsy. During inspiration there is a decrease in the area of the RV pressure curve (orange shaded area) as compared with expiration. The area of the LV pressure curve (yellow shaded area) is unchanged during inspiration as compared with expiration.

were 43 men and 16 women, with a mean age of  $64 \pm 14$  years (range 24 to 99 years). The underlying etiology for the CP based on available clinical data was prior cardiac surgery (28), idiopathic ( $n = 15$ ), radiation therapy ( $n = 9$ ), history of infectious pericarditis ( $n = 4$ ), history of rheumatoid arthritis ( $n = 2$ ), and post-myocardial infarction pericarditis ( $n = 1$ ). Fifty-eight of the 59 patients in group 1 with documented CP had hemodynamic improvement after pericardiectomy (decrease in RAP and increase in cardiac index).

The remaining patients were subsequently thought to have RMD, including the 2 patients who underwent operation but did not have surgical confirmation of CP (group 2). This group included 41 patients (24 men, 17 women) with a mean age of  $64 \pm 13$  years (range 36 to 86 years). Of this group, 23 patients underwent RV myocardial biop-

sies showing tissue histopathology that was compatible with the diagnosis of RMD: amyloid heart disease ( $n = 7$ ), eosinophilic myocardial disease ( $n = 2$ ), mixed connective tissue disease ( $n = 1$ ), endomyocardial fibrosis ( $n = 1$ ), and idiopathic forms of RMD ( $n = 12$ ). The remaining 18 patients had congestive heart failure due to the following myocardial processes: radiation-induced myopathy ( $n = 9$ ), ischemic cardiomyopathy ( $n = 4$ ), end-stage hypertension ( $n = 1$ ), and mixed myocardial-valvular disease ( $n = 4$ ).

**Noninvasive evaluation.** Noninvasive evaluation was performed to specifically evaluate the presence of an abnormal pericardium by magnetic resonance imaging/computed tomographic imaging in 35 of the group 1 patients, with an abnormally thickened pericardium found in 60%. A comprehensive 2-dimensional and Doppler echocardiography was performed in all 59 patients (1,2). Inspiratory variation in mitral flow velocity curves typical of CP was present in 73% and expiratory reversals in the hepatic vein were present in 81%.

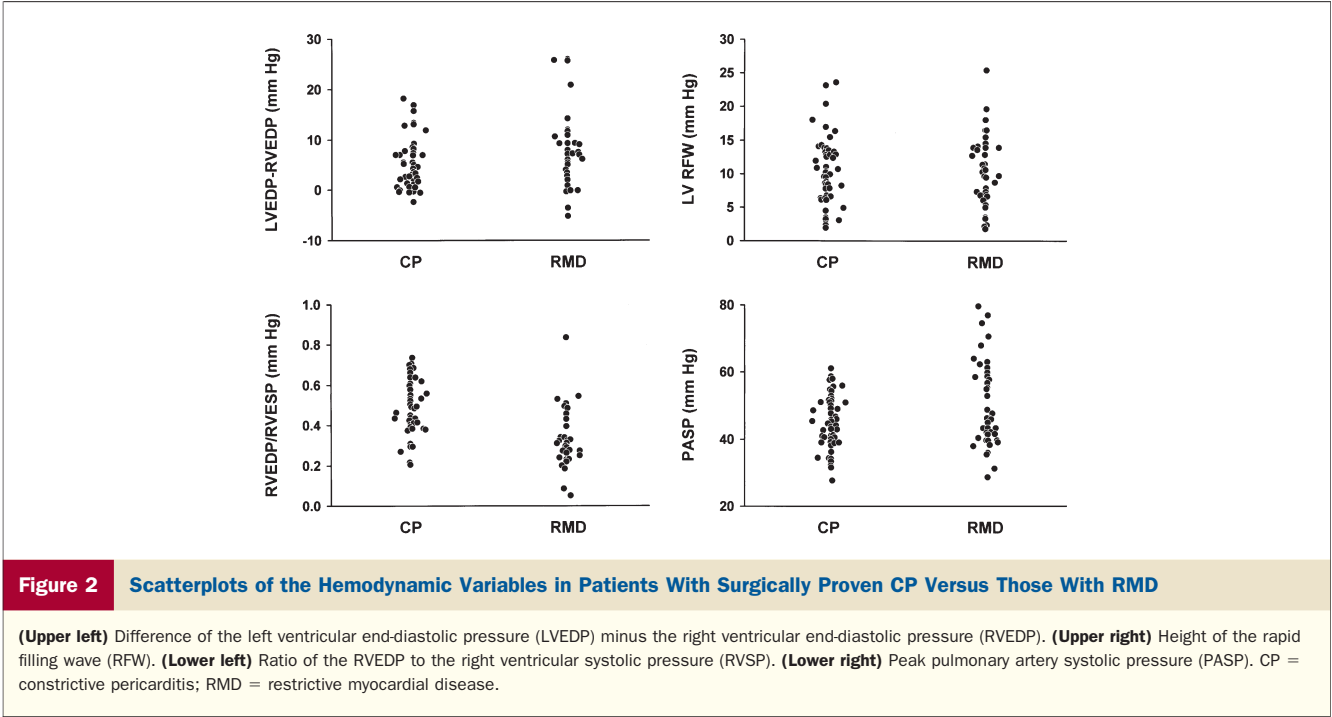
**Hemodynamic data: conventional criteria.** Hemodynamic data obtained at the time of catheterization are shown for patients in both groups (Table 1, Fig. 2). There was a statistically significant difference between group 1 and group 2 when comparing the inspiratory decrease in RAP, difference between LVEDP and RVEDP, and ratio of RVEDP/RV systolic pressure. However, there was overlap present for each of these criteria.

**Hemodynamic criteria: dynamic changes during respiration.** The systolic area index was greater in group 1 than in group 2 ( $1.4 \pm 0.2$  vs.  $0.92 \pm 0.19$ ;  $p < 0.0001$ ), which indicates a larger RV pressure contour and smaller LV pressure contour during inspiration (Fig. 3). There was little overlap between group 1 and group 2 in the systolic area index.

**Comparison of all hemodynamic criteria.** The sensitivity, specificity, positive predictive accuracy, and negative predictive accuracy for all hemodynamic parameters are shown in Table 2. Although there were statistically significant differences in most parameters between group 1 and group 2, the positive predictive accuracy of any of the previously published criteria was  $<75\%$ . The previously published RV index (5) (based on the difference in the peak systolic pressures between inspiration and expiration) had 59% sensitivity and 86% predictive accuracy for identifying patients with CP. The systolic area index (which assesses the change in ventricular pressure area during inspiration and expiration) had 97% sensitivity and 100% predictive accuracy for identifying patients with surgically proven CP.

## Discussion

The diagnosis of CP should always be considered in patients presenting with predominant right heart failure symptoms (3,10,11). Two-dimensional and Doppler echocardiography can rule out other causes of right heart failure, but the differentiation between CP and RMD may be difficult.

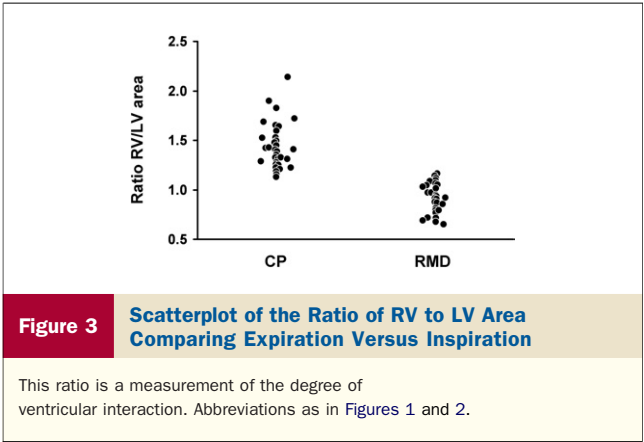


Computed tomography and magnetic resonance imaging can help in detecting an abnormal pericardium (12), but these tests provide anatomical information and do not necessarily reflect the pathophysiological abnormality present. As shown in other studies as well as herein, patients with surgically proven CP may have a normal-appearing pericardium on imaging studies (13). Alternatively patients may have abnormal pericardial thickness in the absence of constriction, especially after radiation therapy or prior cardiac operation.

Cardiac catheterization has been useful in identifying the typical hemodynamic response in CP (4,7-9). These findings consist of early rapid filling and equalization of end-diastolic pressures in all 4 cardiac chambers, but these may also be present in patients with RMD. Other conventional catheterization criteria have included the finding of more severe pulmonary hypertension and a greater difference

between LVEDP and RVEDP in patients with RMD. In this study, there were statistically significant differences in the overall values of these criteria when comparing the group of patients with CP versus those with RMD, but the predictive accuracy of these criteria were of limited value in an individual patient.

It is the dynamic respiratory changes that occur in patients with CP that help differentiate these patients from those with RMD (1,2,5). In patients with CP, there is a dissociation of intrathoracic and intracardiac pressures, which results in a decrease in filling of the LV during inspiration. The constricting pericardium also results in an increase in ventricular interaction, so that there is more RV filling during inspiration. An alternative hypothesis for the discordant changes in RV and LV filling during respiration is a decreased transeptal gradient resulting from an increase in inspiratory flow to the RV, with a decrease in early diastolic suction of the LV. Doppler echocardiography has been used to determine these hemodynamic responses to respiration in patients with CP by examining transmitral and hepatic vein flows. In our practice, cardiac catheterization is not deemed necessary for patients in whom the diagnosis of typical CP can be made on the basis of the clinical presentation and typical features on noninvasive testing, which include a restrictive mitral inflow velocity, typical respiratory changes in transmitral and hepatic vein Doppler velocities, and a normal to increased early diastolic mitral annular tissue velocity (2). Thus the patients with classic findings of CP based on examination and noninvasive testing do not undergo cardiac catheterization, as was the case in 52% of patients in our institution who underwent operation for CP. Conversely, patients with classic infiltra-





tive cardiomyopathies such as amyloid heart disease diagnosed by echocardiography were excluded. There were 550 patients with the diagnosis of amyloid heart disease seen during this time period who did not require catheterization. The patients in this study were those in whom there was still a question of the diagnosis after a comprehensive clinical and noninvasive evaluation, as reflected in the large number of patients who presented with right heart failure after prior radiation therapy or prior open heart surgery, in which there is frequently both myocardial and pericardial disease (3).

We have shown in this study that enhanced ventricular interdependence assessed by cardiac catheterization pressures was useful to diagnose CP in this difficult subgroup of patients, in whom the diagnosis could not be made from extensive clinical and noninvasive testing. Because the area under the ventricular pressure curve reflects the preload of the ventricle, the change in the area of the ventricular pressure curves during respiration can be used to diagnose enhanced ventricular interdependence, which is unique to patients with CP.

There are limitations to this study. This was an observational study performed only on patients who were sent for catheterization for further diagnostic information. This poses a limitation to the true sensitivity and specificity of the catheterization findings for the diagnosis of CP. The RMD group was of a diverse etiology, and we could not entirely rule out the possibility of these patients having an element of concomitant CP. Endomyocardial biopsies were not performed in all patients.

Constrictive pericarditis continues to be a challenging diagnostic dilemma for the clinician, especially in the current era, when there may be both myocardial and pericardial disease present. Although noninvasive modalities have been of benefit in the diagnosis of this entity, there is a subset of patients in whom the diagnosis remains unclear after testing. It is the dynamic respiratory changes reflecting the

enhancement of ventricular interaction assessed at the time of cardiac catheterization that is most useful in making this difficult diagnosis.

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